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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,355	05/03/2001	Donald Morris	032775-047	6889

21839 7590 07/29/2003

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ALEXANDRIA, VA 22313-1404

EXAMINER
LAMBERTSON, DAVID A.

ART UNIT	PAPER NUMBER
1636	14

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,355	MORRIS ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-23 and 26-33* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 8-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01-June-2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 16, 2003 has been entered.

Receipt is acknowledged of a reply and a terminal disclaimer, filed May 16, 2003 as Paper Nos. 11 and 13 in response to the previous Office Action. Amendments were made to the claims. Specifically, claims 7, 24 and 25 were cancelled, and new claims 26-33 were added.

Claims 1-6, 8-23 and 26-33 are pending in the instant application. Claims 1-6 and 8-23 are withdrawn from consideration as being drawn to a non-elected invention by original presentation, as indicated below. Claims 26-33 are ready for examination in the instant application. Any rejection of record in the previous Office Action, Paper No. 10, mailed February 24, 2003, that is not addressed in this action has been withdrawn.

Election/Restrictions

Newly submitted claims 1-6 and 8-23 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the previously elected invention, prior to the filing of a Request for Continued Examination under 37 CFR 1.114, was drawn to a method of selectively removing neoplastic cells from a mixed cellular composition.

Claims 1-6 and 8-23, as amended, read on an entirely different process, specifically a method of transplanting a cellular composition. This method is patentably distinct from the originally elected inventions because the method involves distinct method steps and effects (e.g., the transplantation of cells). Applicant is reminded that it is improper to change inventions during the filing of an RCE.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 1-6 and 8-23 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Claims 26-33 will be examined because the method steps as claimed are substantially similar to the previously elected invention so as to construe them as being drawn to the same elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of a wild type reovirus, a vaccinia virus having mutations in the K3L or E3l genes, a herpes simplex virus having a mutation in the ICP34.5 gene, a parapoxvirus having mutations in the OV20.0L gene, or an adenovirus having mutations in the E1a or E1b genes, does not reasonably provide enablement for all viruses. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. The invention is a method of selectively removing neoplastic cells from a mixed population of cells by adding to the mixed population of cells a virus, which could be any virus including all wild-type viruses, waiting for the lysis of neoplastic cells, and then removing the virus from the population of cells which is now lacking the neoplastic cells.

Scope of the invention. The scope of the invention is very broad, encompassing the use of essentially any virus, including wild-type HIV, herpes, papilloma, and Ebola viruses. The specification describes, in theory, the use of a number of different viruses in the invention, including reovirus, vaccinia virus, herpes simplex virus (HSV), parapoxvirus and adenovirus. However, with the exception of the reovirus, each of the other viruses requires specific mutations in virally encoded genes in order for the virus to have any specificity of infection for neoplastic cells over normal cells. Without these specific mutations, the viruses would infect normal and neoplastic cells indiscriminately. Therefore, claiming the use of any virus is overly broad in scope with respect to the claimed invention.

State of the art. The state of the art reflects the need for mutations in very specific viral genes in order for the viruses to selectively target neoplastic cells, while having little to no effect on the survival of otherwise "normal cells" (see McCormick et al., US Patent No. 5,801,029; see entire document, especially for example column 3, line 35 to column 5, line 22; henceforth McCormick). McCormick teaches that specific mutations in the adenoviral genes, which are responsible for interaction with cellular tumor suppressor proteins such as p53 and the retinoblastoma protein (Rb), are required in order to selectively target neoplastic cells (see for example, the Abstract and column 3, lines 49-53). The same is found to be true regarding a number of other viruses (see for example column 4, line 65 to column 5, line16). However, a wild-type virus (or one not carrying the specific mutations) is capable of infecting a wildtype cell because the specific gene (fro example, p55/E1b in adenovirus) has the capacity to bind to p53 and sequester its anti-viral activities (see for example column 3, lines 35-40). Thus the state of the art appears to indicate that not just any virus can be used to selectively ablate neoplastic cells in a mixed composition of neoplastic and normal cells, but rather, a virus having a specific mutation is required.

Number of working examples. The instant specification provides only one working example, in which a wild-type reovirus is used to specifically ablate ras-activated neoplastic cells in a mixed population of cells, *in vitro*. However, there is evidence in the prior art of other examples that have been found to be enabled *in vivo*, such as the use of adenovirus E1a or E1b mutants, human papillomavirus E6 and E7 mutants, etc. (see McCormick et al., US Patent No. 5,801,029; see entire document, especially for example column 3, line 35 to column 5, line 22), and these would presumably work *in vitro* as well.

Guidance provided by applicant. The instant specification provides guidance with regard to the use of a wild-type reovirus, and some specific mutated viruses such as a vaccinia virus having mutations in the K3L or E3l genes, a herpes simplex virus having a mutation in the ICP34.5 gene, a parapoxvirus having mutations in the OV20.0L gene, or an adenovirus having mutations in the E1a or E1b genes. The instant specification suggests using these viruses to selectively eliminate neoplastic cells from a mixed population of cells *in vitro*. However, the instant specification does not expand on these viruses to say what other wild-type viruses could be used for the selective ablation of neoplastic cells, nor does the instant specification expand on what other mutated viruses would also selectively remove neoplastic cells from a mixed population of cells.

Level of skill in the art. The level of skill in the art for using mutant viruses to selectively ablate neoplastic cells in vivo is known in the art. However, the level of skill in the art regarding the use of any virus to selectively remove neoplastic cells is underdeveloped.

Unpredictability of the art. The art is unpredictable for several reasons. First, there is a body of evidence suggesting that specific mutations must be made in a virus in order to selectively target neoplastic cells (see McCormick as cited above). Without any teachings as to what wild-type viruses besides a reovirus could be used to selectively remove neoplastic cells from a mixed population of cells, the skilled artisan would be placed in a situation where undue and unpredictable trial and error experimentation would be required to identify other wild-type viruses capable of selectively killing neoplastic cells. Second, there are no teachings in either the prior art or the instant specification as to what other mutations can be made to a virus, besides a vaccinia virus having mutations in the K3L or E3l genes, a herpes simplex virus having a

mutation in the ICP34.5 gene, a parapoxvirus having mutations in the OV20.0L gene, or an adenovirus having mutations in the E1a or E1b genes, whereby the mutated virus would be capable of selectively killing neoplastic cells. Without teachings regarding new wild-type viruses that are capable of selectively ablating neoplastic cells, or additional mutations besides those that are already taught in the art for the same purpose, the skilled artisan would be reduced to practice undue and unpredictable trial and error experimentation to uncover these wild-type and mutant viruses. As a result, the invention is not enabled for the full scope of the invention for which it is claimed. Rather, the invention is enabled for the use of a reovirus, a vaccinia virus having mutations in the K3L or E3l genes, a herpes simplex virus having a mutation in the ICP34.5 gene, a parapoxvirus having mutations in the OV20.0L gene, or an adenovirus having mutations in the E1a or E1b genes, for the purpose of selectively ablating neoplastic cells from a mixed population of cells.

Claims 26-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims the ability to selectively remove neoplastic cells from a mixed population of cells by adding any virus to the population of cells. The claims read on a broad genus of viruses that can be used in the method, including any wild-type virus.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by

disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims a virus capable of selectively killing neoplastic cells by function only, without any disclosed or known correlation between the elements and their function. The specification only provides teachings regarding a wild-type reovirus, a vaccinia virus having mutations in the K3L or E3l genes, a herpes simplex virus having a mutation in the ICP34.5 gene, a parapoxvirus having mutations in the OV20.0L gene, or an adenovirus having mutations in the E1a or E1b genes. The specification does not teach additional wild-type viruses which can selectively kill neoplastic cells, or what structure-function properties of a reovirus result in this unique ability so that other viruses could readily be identified based on those properties. Additionally, the instant specification does not teach what mutations can be made to a virus, other than a vaccinia virus having mutations in the K3L or E3l genes, a herpes simplex virus having a mutation in the ICP34.5 gene, a parapoxvirus having mutations in the OV20.0L gene, or an adenovirus having mutations in the E1a or E1b genes, so that the virus will selectively ablate neoplastic cells. Therefore, the skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant specification because the specification only discloses specific examples of viruses that specifically kill neoplastic cells.

The prior art does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. While the prior art does provide guidance with respect to several mutants that are capable of selectively killing neoplastic cells, those are the same mutants that are discussed in the instant specification. However, the prior art does not provide any evidence of additional wild-type viruses that are capable of selectively killing neoplastic cells besides the reovirus, nor does the prior art teach additional mutant viruses besides those that are specifically discussed in the instant specification. Thus the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

The skilled artisan would not be able to envision the claimed invention by relying on the teachings of the prior art or the instant specification. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 does not recite a method step in the claim that recapitulates the method as set forth in the preamble of the claim. Specifically, there is no step wherein the cellular composition with a reduced amount of neoplastic cells is obtained (i.e., collected, isolated, etc.). Because

there is no ultimate step in the method as claimed, the method is open-ended and therefore indefinite.

Claims 30, 32 and 33 recite the limitation "cellular composition" in the first line of the claims. There is insufficient antecedent basis for this limitation in the claim because it is unclear what cellular composition, the mixed cellular composition or the cellular composition with a reduced amount of neoplastic cells, is being referred to.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-5, 7, 8, 15, 16 and 21 of copending Application No. 09/847,356 (US 2002/0006398; cited previously; henceforth the '356 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons:

1. Claim 26 is a genus claim that is anticipated by the species claims 15, 16 and 19 of the '356 application. Specifically, instant claim 26 reads on the use of any virus to produce a cellular

composition that is substantially free of neoplastic cells, and claims 15, 16 and 19 of the '356 application read specifically on the use of a reovirus to produce a cellular composition that is substantially free of neoplastic cells. Because a reovirus is a virus, claims 15, 16 and 19 of the '356 application anticipate the claim 26 of the instant application.

2. Claims 27-32 of the instant application are obvious in view of claims 15 or 16 in further view of claims 2-5, 7, 8 of the '356 application. Specifically, claims 27-32 are drawn to the use of specific sources for the cellular composition that is to be treated by the method steps set forth in claim 26, discussed above. Claims 2-5, 7 and 8 of the '356 application are dependent on claim 1, and recite the same sources for the cellular composition that are recited in claims 27-32 of the instant application. However, claims 2-5, 7 and 8 do not comprise the limitation wherein the virus is removed from the treated composition. Claims 15 and 16 of the '356 application are drawn substantially to the same subject matter of claim 26 in the instant application, and claims 15 and 16 both depend from claim 1 of the '356 application, similarly to claims 2-5, 7 and 8. It would have been obvious to combine the limitations of claims 2-5, 7 and 8 with those of claims 15 and 16 because the claims each depend from the same claim, and are logically applicable in combination. Motivation to combine these limitations comes from the desire to cover the entire scope of the disclosed invention. Absent evidence to the contrary, there would be a reasonable expectation of success when practicing the combined teachings set forth above.

3. Claim 33 of the instant invention is obvious in view of claims 15 or 16 in further view of claim 21 of the '356 application. Specifically, claim 33 is drawn to the composition obtained by the method of claim 26. Claim 21 of the '356 application is drawn to the composition obtained by the method of claim 1. However, claim 21 does not recite the limitation wherein the virus is

removed from the treated composition. As indicated previously, claims 15 and 16 are drawn substantially to the same subject matter of claim 26 in the instant application, and claims 15 and 16 both depend from claim 1 of the '356 application. It would have been obvious to combine the limitations of claim 21 with those of claims 15 and 16 because the claims each depend from the same claim, and are logically applicable in combination. Motivation to combine these limitations comes from the desire to cover the entire scope of the disclosed invention. Absent evidence to the contrary, there would be a reasonable expectation of success when practicing the combined teachings set forth above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is noted that applicant has previously filed a terminal disclaimer between the instant application and copending Application No. 09/847,356. However, the claims that were previous provisionally rejected are now withdrawn as being drawn to a non-elected invention by original presentation, and the rejection no longer applies to these claims. However, the rejection now applies to the newly added claims, and must therefore be made of record. Acknowledgement by applicant regarding this issue and a statement that the previously filed terminal disclaimer is enforceable with respect to the newly rejected claims would be sufficient to overcome the rejection without the need for a new terminal disclaimer.

Response to Arguments

Applicant's arguments with respect to claims 1-6 and 8-23 have been considered but are moot in view of the fact that the claims are now drawn to an invention that is non-elected by

original presentation. Thus, the arguments will not be addressed with respect to the examined claims.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
July 25, 2003

DAVID GUZO
PRIMARY EXAMINER